Health Care Delivery

Survival Following Cardiac Transplantation—What Are Acceptable Standards?

DALE G. RENLUND, MD; MICHAEL R. BRISTOW, MD, PhD; NELSON A. BURTON, MD; KENT W. JONES, MD; S. V. KARWANDE, MD, *and* WILLIAM A. GAY, Jr, MD, *Salt Lake City*

In an 18-month period, 50 orthotopic cardiac transplantations were done in Utah in 48 patients with end-stage heart failure. The 12-month actuarial survival was 98%, indicating that successful cardiac transplantation can be done in a newly established program and that the intermountain West has an adequate supply of potential recipients and donors for a moderate- to high-volume program. Furthermore, the administration of cardiac transplantation in a setting of other treatment modalities of heart failure in a multi-institutional program that crosses private practice-academic barriers is feasible. Results such as these need to be considered by the federal government as it establishes eligibility criteria for centers to be approved for Medicare-funded cardiac transplantation.

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Cardiac transplantation remains a costly, labor-intensive and complicated treatment for end-stage cardiac dysfunction.[1] During 1985 the number of institutions in the United States doing cardiac transplantation increased from 37 to 74 and the number of these procedures increased nearly fivefold.[2] It is generally held that successful cardiac transplant programs must have a reasonable volume of patients, necessitating their location in a large metropolitan area; have been established for some period of time so that the "learning curve" is passed; be administered consistently so that only one hospital in a multi-institutional program does the procedure, and be separated from other treatment modalities of end-stage heart failure. Inasmuch as the federal government is presently considering several of these criteria in determining which centers will be eligible for Medicare funding of cardiac transplantation,[3] a consideration of their relative importance is timely.

Ostensibly the government's involvement relates to the notion that cardiac transplantation requires a scarce resource, the health-care dollar, and that regulation of its expenditure is appropriate.[4] Focus on the financial concerns, however, may ignore important ethical considerations. The limiting resource in cardiac transplantation is the availability of donor organs. When a significantly higher success rate is achieved in some institutions than in others, transplantation at the inferior institutions represents wastage of a resource that is in extremely scarce supply. The success rate in transplantation also affects cost, as the treatment of complications carries an increased output of health care dollars and loss of potential productivity. Therefore, it seems desirable that strict criteria for success in cardiac transplantation be used by any regulatory body attempting to allocate scarce resources of all types.

With the first cardiac transplantation done in the state of Utah 18 months ago,[5] the testing of the following assertions began: that successful results could be obtained without a lengthy "learning curve" if sufficient preparation and expertise were assured; that there existed a large volume of eligible recipients and donors in the intermountain West; that a consistent program could be administered in three institutions, blending academic and private practice interests and enabling the use of more resources than any single institution could afford, and that it is advantageous to do cardiac transplantation in a setting of other treatment modalities of heart failure. Our initial experience challenges some of the previously held notions about cardiac transplantation and suggests that the standard of success in cardiac transplantation should be higher than is generally considered acceptable.

Methods

Hospitals

The three hospitals used for the cardiac transplantations in Utah are in the University of Utah's teaching hospital system. They consist of LDS Hospital, a 520-bed private facility; the University of Utah Hospital, a 400-bed patient care facility on the campus of the University of Utah, and the Veterans Administration Medical Center (VAMC), a 367-bed patient care hospital. All three hospitals are modern, tertiary referral hospitals drawing patients from the entire intermountain West. Their respective referral systems encompass the vast majority of patients in Utah, southern and eastern Idaho, central and

From the UTAH Cardiac Transplant Program, Division of Cardiology, University of Utah School of Medicine Medical Center, the Veterans Administration Medical Center and the LDS Hospital, Salt Lake City. The personnel of the Utah transplant-affiliated-hospitals Cardiac Transplant Program—*Cardiovascular Surgeons:* Nelson A. Burton, MD; Donald B. Doty, MD; William A. Gay, Jr, MD, (Surgical Director); Kent W. Jones, MD; S. V. Karwande, MD; *Cardiologists:* Jeffrey L. Anderson, MD; Michael R. Bristow, MD, PhD, (Medical Director); J. Lee Burke, MD; Clement C. Eiswirth, MD; Edward M. Gilbert, MD; Donald L. Lappe, MD; Jeffrey A. Laser, MD; John B. O'Connell, MD; Dale G. Renlund, MD; Theophilos J. Tsagaris, MD; Sherman G. Sorensen, MD; Richard B. Sutton, MD; *Transplant Coordinators:* Jan Curtis, RN; Linda A. Freedman, RN; Colette M. Herrick, RN, (Chief Coordinator); Patrice C. Mealey, RN; Cherylyn Robinson, RN; *Transplant Surgical Coordinator:* William Wong, PA; *Pathologists:* Thomas V. Colby, MD; M. Elizabeth Hammond, MD; Randall G. Lee, MD.

Reprint requests to Dale G. Renlund, MD, Division of Cardiology, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132.

ABBREVIATIONS USED IN TEXT

ATG = antithymocyte globulin
IV = intravenously
PVR = pulmonary vascular resistance
VAMC = Veterans Administration Medical Center

eastern Nevada, southern and western Wyoming and southeast Montana.

Administration

Overall direction of the program is provided through an executive committee consisting of a medical director, a surgical director and representatives from each hospital (see Figure 1). This executive committee is composed of University of Utah faculty along with private cardiac surgeons and cardiologists at LDS Hospital. The goals of the program were to establish a clinical and basic research program dedicated to solving problems in transplantation and investigating mechanisms responsible for heart muscle disease and heart failure, and to provide a clinical service to patients in the intermountain West. The executive committee meets at least weekly to ensure progress towards these goals. It reviews and prioritizes cases, is updated on the clinical course of inpatients and outpatients with transplants, addresses concerns from each hospital and ensures consistency in patient care at each participating hospital.

Heart failure clinics were established for the three institutions. In these settings, the most appropriate of many treatment modalities could be selected for individual patients, ranging from conventional medical treatment, referral for revascularization or surgical intervention other than cardiac transplantation, investigational medications or cardiac transplantation. Patients who met the following criteria were considered for transplantation.

- Severe, New York Heart Association class IV cardiac dysfunction unremedial to surgical treatment other than cardiac replacement.
- Limited life expectancy, with a one-year survival estimated to be less than 50%.
- Age younger than 65 years.
- No systemic illness other than abnormalities related to heart failure.
- Emotional stability.
- The presence of an adequate psychosocial support system.
- Absence of the following:
  1. Pulmonary hypertension (pulmonary vascular resistance [PVR] more than 8 Wood units or a PVR of more than 6 Wood units with inability of sodium nitroprusside infusion to reduce the PVR to below 3 Wood units or inability to reduce pulmonary artery systolic pressure below 50 mm of mercury).
  2. Severe irreversible hepatic, renal or pulmonary disease.
  3. Active systemic or pulmonary infection.
  4. Recent pulmonary infarction.
  5. Diabetes mellitus requiring insulin.
  6. History of uncontrollable hypertension.
  7. Systemic vascular or cerebrovascular disease.
  8. Active peptic ulcer disease.
  9. Unresolved substance abuse.

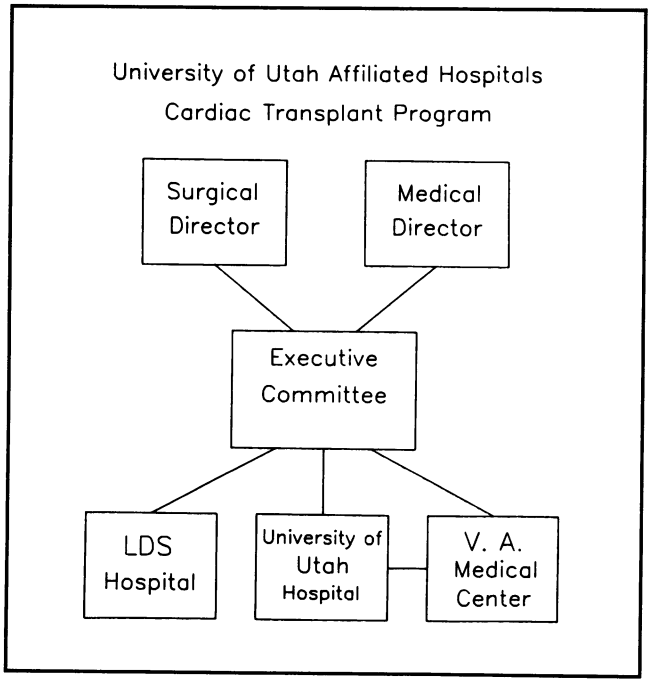

Figure 1.—Administrative structure of Utah Transplant Affiliated Hospitals Cardiac Transplant Program. The program is directed by an executive committee composed of the officers indicated above.

Preoperative and postoperative medical care including immunosuppressive therapy and posthospital discharge care and surveillance are provided by the transplant medical team using the heart failure clinic as a base for all outpatient work. Graft placement and organ harvest are done by a five-member cardiovascular surgery team consisting of two LDS Hospital surgeons, two Utah University Hospital surgeons and one VAMC surgeon. Donors are screened by a member of the executive committee once potential donor brain death has been declared. Laboratory data that are routinely acquired include hepatitis screening, human immunodeficiency virus screening, chest x-ray film, arterial blood gas determinations and electrocardiogram. An echocardiogram is additionally done[6] if possible. Also, the time, date and type of accident are ascertained along with the types of injuries sustained. Before approval for use as a donor, the current medications, in particular vasopressors, with their dosage and duration of treatment are determined. Diabetes insipidus is treated and blood pressure, heart rate and volume state are optimized.

Immunosuppression

During the 18-month period, three immunosuppressive protocols were used, dictated primarily on the basis of the supply of equine antithymocyte globulin (ATG) (Atgam, Upjohn Pharmaceutical Company):

Protocol 1. The use of ATG without steroid pulse
Protocol 2. The use of ATG with steroid pulse
Protocol 3. The use of OK T3 monoclonal antibody with steroid pulse.

In both protocols 1 and 2, patients preoperatively received cyclosporine, 3 mg per kg body weight given intravenously (IV); ATG, 10 mg per kg IV, and azathioprine sodium, 4 mg per kg IV. Intraoperatively, methylprednisolone sodium succinate, 500 mg, was administered. Postoperatively, patients received methylprednisolone, 125 mg IV every eight hours for three doses; azathioprine, 2 mg per kg given IV or orally

per day; ATG, 10 mg per kg given IV daily for seven days; cyclosporine, 2 mg per kg IV on postoperative day 1 and then 12 mg per kg per day given orally in two divided doses beginning on day 2. The cyclosporine dose was then adjusted to maintain a level of 200 to 300 ng per ml for 30 days and then further adjusted to maintain a level of 75 to 200 ng per ml thereafter.

Protocol 2 differed from protocol 1 in that on day 8, prednisone, 1 mg per kg, was administered daily for seven days and then tapered over two weeks.

Protocol 3 differed in that preoperatively only azathioprine, 4 mg per kg given IV, was used. Methylprednisolone was administered intraoperatively at the same dose of 500 mg. Postoperatively, methylprednisolone, 125 mg, was administered every eight hours for three doses and then 5 mg OK T3 was given IV daily for 14 days. Azathioprine was administered daily at 2 mg per kg postoperatively. Cyclosporine was first begun on day 4 at a dose of 6 mg per kg per day orally in two divided doses and adjusted to a serum concentration of 100 to 200 ng per ml. On day 15, prednisone, 1 mg per kg, was given in two divided doses for seven additional days and then tapered over two weeks.

Since patient 8, all patients have been randomly selected to receive vincristine sulfate, 0.025 mg per kg for eight doses, or no vincristine (beginning on day 9 for protocols 1 and 2 and day 17 for protocol 3).

A biopsy was taken weekly for six to eight weeks and then the frequency of biopsies was decreased depending on the state of cardiac rejection. For treatment of rejection, high-dose methylprednisolone therapy was used, with or without ATG, OK T3 or rabbit antilymphocyte globulin, followed by tapering doses of prednisone. Following the prophylactic use of prednisone, as in protocols 2 and 3, or after its use in the treament of rejection, the prednisone dosage was tapered and discontinued unless cardiac rejection recurred. This tapering and discontinuing, if possible, was attempted repeatedly until three rejection episodes had occurred in a particular patient, at which point the prednisone dosage was subsequently tapered to a low maintenance dose.

Results

From March 8, 1985, to September 7, 1986, we evaluated 153 patients in the combined heart failure clinics. Three underwent other surgical procedures (one revascularization, two a valvular operation), 67 were assigned to experimental therapy, 35 were directly assigned to cardiac transplantation with conventional therapy until the time of transplantation and 48 were treated conventionally without being assigned to transplantation. Of the patients assigned to experimental therapy, 19 were subsequently assigned to cardiac transplantation. In the initial evaluation of three of these patients, it had been felt that they had inadequate emotional stability or insufficient family support to undergo transplantation. After observing them for the duration of the particular investigational study, however, the initial evaluation was found to be in error. This would likely not have been noted without the follow-up afforded by an investigational study. Of those in whom conventional therapy was used, none were subsequently assigned to transplantation.

Table 1 shows the age, sex, cause of heart failure, average number of previous heart operations, pretransplant ejection fraction and the number requiring pretransplant hemodynamic support in 48 patients who underwent cardiac trans-

TABLE 1.—*Heart Transplant Patient Characteristics in 48 Patients*

Patient Characteristics	Values
Age, years	45.0±12.4*
Median	48
>50 years old, %	44
Range	16 to 63
Sex	
Male, No. (%)	43 (89.5)
Female, No. (%)	5 (10.5)
Cause of heart failure, No. (%)	
Idiopathic dilated cardiomyopathy	25 (52.1)
Coronary artery disease-induced cardiomyopathy	19 (39.5)
Valvular heart disease-induced cardiomyopathy	2 (4.2)
Hypertrophic cardiomyopathy	1 (2.1)
Acute myocarditis	1 (2.1)
Previous chest operation, No.	0.5±0.77*
Range	0 to 3
Pretransplant ejection fraction	0.18±0.05*†
Range	0.10 to 0.27*†
Pretransplant hemodynamic support	
Inotropic agents (other than digoxin)‡	18
Intra-aortic balloon counterpulsation	4

*Mean ± standard deviation.
†Does not include a patient with hypertrophic cardiomyopathy whose ejection fraction was greater than 70%.
‡Inotropic agents: dopamine, dobutamine, enoximone, norepinephrine (levarterenol) bitartrate.

TABLE 2.—*Transplant Recipients' State of Residence*

State	Number	Percent
Utah	16	33
Nevada	8	17
Idaho	8	17
Montana	6	12
Wyoming	4	8
Alaska	3	6
Oregon	1	2
Oklahoma	1	2
Missouri	1	2

TABLE 3.—*Distribution and Survival of Cardiac Transplant Recipients Among the Utah Transplant Affiliated Hospitals*

Category	UUH	LDSH	VAMC	Total
Transplants	24	14	12	50
Patients	23	13	12	48
Survivors	22	13	12	47
12-Month actuarial survival, %	96	100	100	98

LDSH=LDS Hospital, UUH=University of Utah Medical Center, VAMC=Salt Lake City Veterans Administration Medical Center

TABLE 4.—*Transplant Recipient Distribution Among Immunosuppressive Protocols and Incidence of Serious Infection*

Protocol*	Total Enrolled	Serious Infections	
		Number	Percent
1	16	4	25
2	17	6	35
3	15	4	27

*Protocol 1: equine antithymocyte globulin (ATG) given without steroid pulse; protocol 2: ATG given with steroid pulse; protocol 3: OK T3 given with steroid pulse.

plantation. It seems that this patient group does not represent a select group of young, healthy patients in whom survival would be expected to be higher. This is supported by the finding that 18 patients were hemodynamically supported preoperatively (4 with intra-aortic balloon pump and inotropic agents, 14 with inotropic agents alone).

Table 2 shows the state of residence of the patients who received transplants. Although 33% are from Utah, other intermountain states are well represented.

During this time period, of the 54 assigned to transplantation, 50 transplants were done in 48 persons (see Table 3). Two patients required retransplantation due to refractory rejection and hemodynamic compromise. There were six deaths in the transplant waiting list, and 1 of the 48 transplant patients succumbed to rejection. This patient died on day 9 of protocol 1. The 12-month actuarial survival is 98% in those transplanted—with an average follow-up of 8 ± 6 months and a range of 0.5 to 18 months—and 87% in those approved for transplantation.

Table 4 shows the number of patients enrolled in each protocol and the number of serious infections in each group. There is no difference in the three protocols with regard to serious infections. These infections were cytomegalovirus pneumonitis (one), *Pneumocystis carinii* pneumonia (two), *Legionella* pneumonia (two), *Staphylococcus epidermidis* pneumonia (two), pneumococcal pneumonia (three), *Pseudomonas* bronchiolitis (one), *Staphylococcus aureus* pulmonary abscess (two), *S aureus* mediastinitis (two), abdominal wound *Pseudomonas* (one) and *Pseudomonas* urinary tract infection (one).

In the 42 patients who are presently on maintenance immunosuppressive regimens, 20 (48%) have had their steroid therapy successfully tapered off. Overall, there have been 66 episodes of moderate rejection (defined as the presence of interstitial lymphocytic infiltrates with or without necrosis) or of greater severity. Protocol 3 has clearly been associated with less rejection. Complete discussions of the immunosuppression results are presented elsewhere.[7,8]

Discussion

The results indicate that excellent survival can be achieved in a new cardiac transplantation program. This is possible because the science and art of transplantation have been elucidated in well-established programs such as that at Stanford University.[9] To accept a high mortality rate in new programs, simply because they are new, seems inappropriate. In fact, the Medicare-proposed one-year minimal actuarial survival of 70% appears intolerably low for any program.

Our experience also shows that successful transplantation need not be carried out in a large metropolitan area. It is also clear that volume need not be high in individual hospitals to achieve excellent results if the team caring for patients has experience with a relatively large population. The total volume of cases in the Utah program was high from the beginning, reflecting a relatively large referral base and an adequate donor supply in the intermountain West.

It is doubtful whether any individual hospital in the group could have carried out 50 transplants in the past 18 months. It was in an effort to consolidate resources and minimize competition for donor hearts that the three-hospital approach was undertaken.[5] Because a common medical team cares for patients in all hospitals, patient care is uniform. Private practitioners and academic faculty interests have been able to combine in this effort to obtain the present results.

Clearly it is not detrimental to administratively incorporate clinical cardiac transplantation in a setting that deals with all treatment modalities for heart failure. In fact, our experience suggests that this may be the best approach. Cardiologists, nurse coordinators and ancillary staff are thereby well acquainted with the patients before transplantation, and the patients are well acquainted with them. Medication compliance, emotional stability and family support systems can be extensively evaluated during nontransplant therapy. Patients in whom cardiac dysfunction is not severe enough to be considered for transplantation can be prospectively observed carefully for signs of deterioration.

Given our experience and the experience of certain other recently established programs,[10] it would seem that a survival rate of less than 80% in 12 months of any program is unacceptable. Furthermore, given the constraints that exist in donor supply, if the survival rate in a well-established program does not approach 90%, reasons for this excessively high mortality should be sought, identified and corrected. It can be argued that to do this procedure with a lesser standard is unethical, as a precious and limited commodity (donor hearts) is wasted by such results.

In summary, high mortality is not intrinsic to new cardiac transplant programs and should be unacceptable in any cardiac transplant program. The intermountain West has an adequate supply of potential recipients and donors for a cardiac transplant program with a moderate to high volume. A multiinstitutional program that crosses private practice-academic barriers is feasible. Finally, cardiac transplantation complies rationally and optimally with heart failure research goals, and the combination of these two programs under one administrative unit likely enhances the outcome of each.

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